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Associations between birth size and later height from infancy through adulthood: An individual based pooled analysis of 28 twin cohorts participating in the CODATwins project[☆]

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ABSTRACT

Background: There is evidence that birth size is positively associated with height in later life, but it remains unclear whether this is explained by genetic factors or the intrauterine environment.
Aim: To analyze the associations of birth weight, length and ponderal index with height from infancy through adulthood within mono- and dizygotic twin pairs, which provides insights into the role of genetic and environmental individual-specific factors.
Methods: This study is based on the data from 28 twin cohorts in 17 countries. The pooled data included 41,852 complete twin pairs (55% *monozygotic* and 45% same-sex *dizygotic*) with information on birth weight and a total of 112,409 paired height measurements at ages ranging from 1 to 69 years. Birth length was available for 19,881 complete twin pairs, with a total of 72,692 paired height measurements. The association between birth size and later height was analyzed at both the individual and within-pair level by linear regression analyses.
Results: Within twin pairs, regression coefficients showed that a 1-kg increase in birth weight and a 1-cm increase in birth length were associated with 1.14–4.25 cm and 0.18–0.90 cm taller height, respectively. The magnitude of the associations was generally greater within *dizygotic* than within *monozygotic* twin pairs, and this difference between zygosities was more pronounced for birth length.
Conclusion: Both genetic and individual-specific environmental factors play a role in the association between birth size and later height from infancy to adulthood, with a larger role for genetics in the association with birth length than with birth weight.

1. Introduction

Height is inversely related to all-cause mortality but shows heterogeneous relationships with cause-specific morbidity and mortality [1–3]. For example, there is a well-established association with incidence of cardiovascular diseases (CVD) [1,3]; shorter individuals both in childhood and adulthood have a higher risk of coronary heart disease [4–6]. In contrast, taller people are at a greater risk of death from several specific cancers [3,7]. Epidemiological studies have shown a positive association between size at birth (i.e. birth weight or birth length) and height in childhood [8], adolescence [9,10] and adulthood [11–13]. Similar findings have been observed in studies restricted to children of low birth weight or born small for gestational age [14–16]. The mechanisms underlying this association are, however, still poorly understood. One explanation involves the critical role of intrauterine environment in childhood growth [17,18], but it is unclear to what extent the associations between birth size and later height reflect early developmental factors in the intrauterine environment or whether they are explained by common genetic factors affecting body size already in fetal life.

Twins provide a natural experimental design that offers an opportunity to shed light into the mechanisms underlying the association between birth size and later height [19,20]. Twins come from the same family, share the same maternal environment, have the same gestational age, and in the case of monozygotic (MZ) twins, they share the same genomic sequence, whereas dizygotic (DZ) twins share, on average, 50% of genes identical-by-descent. However, each fetus has its own fetoplacental environmental conditions, such as supply of nutrients and oxygen, which may differ substantially from that of its co-twin [21]. The association between the intra-pair differences in birth size and intra-pair differences in later height cannot be attributed to shared family factors, such as maternal nutrition, smoking during pregnancy, parental education or socio-economic status. Further, differences within MZ pairs cannot be attributed to genetic factors. The comparison of intra-pair associations in MZ and DZ twins is, thus, a strong design to distinguish within-family effects, that is, the non-shared environment and genetic differences between co-twins. Differences in birth size and later height within MZ pairs can only be influenced by environmental factors that are unique to individuals (i.e. the individual-specific intrauterine environment), while differences within DZ pairs can also be influenced by genetic factors [19,20]. Thus, a stronger association within DZ than MZ twin pairs is taken as evidence that the relationship between birth size and later height is explained, at least in part, by genetic factors [19].

Twin studies in late adolescence and adulthood have shown that intra-pair differences in birth size are positively associated with intra-pair differences in later height [22–27]; i.e. the heavier or longer co-twin at birth will also be the taller one later in life. These associations between birth size and height were generally greater in DZ than in MZ twins, suggesting that both the individual-specific intrauterine environment and genetic factors are involved [23–26]. However, it is not known whether these effects vary in their importance by sex or age, particularly in childhood. Moreover, studies in singletons have shown that height is more strongly associated with birth length than with birth weight [12,13], suggesting that part of the association with birth weight is driven by birth length. Whether these associations are differently affected by genetic and environmental factors is not clear [24,26]. To address these questions, we analyzed the association between birth size (weight, length and ponderal index (PI)) and later height from infancy to adulthood in MZ and DZ twins of both sexes, at both the individual and within-pair level, in a multinational database of 28 twin cohorts from 17 countries.

2. Material and methods

2.1. Sample

This study is based on the data from the COllaborative project of Development of Anthropometrical measures in Twins (CODATwins), which aims to pool data from all twin projects in the world with information on height and weight [28]. Information on birth weight and length was available in 28 and 15 cohorts, respectively. The participating twin cohorts are identified in Table 1 (footnote) and were previously described in detail [28,29].

In the original database, there were 124,475 twin individuals with information on birth weight and later height measurements from ages 1 to 69 years. After excluding 80 individuals with extreme birth weight of < 0.5 or > 5 kg, there were 124,395 individuals with a total of 378,796 height measurements throughout the life course. Age was classified to single-year age groups from age 1 to 19 years (e.g. age 1 refers to 0.5–1.5 years range) and one adult age group (20–69 years); height measurements at ages ≥70 years were excluded because individuals in old age are more likely to develop osteoporosis leading to shorter height. Implausible values and outliers were checked by visual inspection of histograms for each age and sex group and were removed (< 0.2% of the measurements) to obtain an approximately normal distribution, resulting in 378,284 measurements. To confirm that all analyses are based on independent observations, we selected one height measure per individual in each age group by keeping the measurement at the youngest age (removing 10% of the measurements), which left 339,097 observations from 124,041 individuals. We next excluded unmatched pairs (without data on their co-twins) resulting in 156,084 paired observations. Because of the effects of sex differences within pairs on both birth size and height, opposite-sex dizygotic twin pairs were excluded (43,409 paired observations). Intra-pair differences in birth weight and later height were checked by visual inspection of histograms; we removed extreme intra-pair differences (implausible values/outliers) of birth weight > 1.7 kg (92 paired observations) and

Table 1
Descriptive statistics of birth size and later height by zygosity, age and sex.

	Males						Females					
	MZ			DZ			MZ			DZ		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Birth weight (kg)	20,804	2.53	0.55	20,124	2.61	0.57	23,240	2.42	0.53	19,536	2.52	0.55
Birth length (cm)	10,720	46.9	3.49	10,172	47.4	3.49	10,510	46.3	3.49	8360	46.8	3.46
Ponderal index (kg/m^3)	10,594	24.4	3.05	10,034	24.5	3.07	10,378	24.3	3.24	8218	24.5	3.22
Height (cm)												
Age 1	5732	73.3	4.62	5344	74.2	4.36	6250	72.0	4.71	4946	72.8	4.40
Age 2	4588	86.3	4.37	4422	86.9	4.28	4798	85.1	4.42	3882	85.9	4.33
Age 3	5542	95.8	4.43	5446	96.4	4.32	6292	94.8	4.40	5100	95.4	4.55
Age 4	3184	102.1	5.16	3166	102.5	5.20	3388	101.1	5.04	2954	101.3	5.14
Age 5	2514	110.9	5.93	2420	111.5	5.99	2688	110.2	6.01	2134	110.8	6.21
Age 6	1120	114.2	6.34	818	115.1	6.67	1072	113.2	5.80	662	114.2	7.07
Age 7	4590	123.6	6.59	4106	124.7	6.52	5110	122.9	6.44	3986	123.8	6.64
Age 8	2098	127.6	6.24	1598	129.1	6.47	2190	127.0	6.39	1352	127.9	6.74
Age 9	2002	133.0	6.94	1566	134.0	6.93	2044	132.0	6.88	1352	133.7	7.06
Age 10	3796	140.1	7.13	3276	141.5	7.12	4156	139.9	7.39	3014	141.0	7.19
Age 11	3040	143.6	7.06	2484	144.9	7.25	3278	144.2	7.31	2152	145.3	7.78
Age 12	3986	151.1	8.18	3122	152.2	7.76	4204	152.2	8.04	3078	153.0	8.10
Age 13	1294	158.0	9.40	1150	158.8	9.24	1306	157.4	7.41	956	158.6	7.92
Age 14	2168	165.5	8.99	1956	166.0	8.79	2556	161.9	6.68	2010	162.6	6.76
Age 15	1334	172.2	8.43	1192	172.5	8.46	1318	165.0	6.83	1100	164.7	7.00
Age 16	1660	175.9	7.54	1596	176.2	7.48	2066	164.5	6.47	1774	165.4	6.59
Age 17	1872	178.0	7.27	1950	178.2	7.01	2524	165.7	6.57	2040	166.3	6.41
Age 18	2028	179.1	6.89	1696	179.2	6.76	1382	166.5	6.54	1144	166.6	6.58
Age 19	814	179.3	6.90	780	180.3	6.47	996	166.4	6.56	738	168.0	6.40
Age 20–69	5290	178.6	6.89	4220	179.6	6.57	6860	164.2	6.40	5006	165.2	6.26

Names list of the participating twin cohorts in this study: Australian Twin Registry, Boston University Twin Project[a], Carolina African American Twin Study of Aging, Child and Adolescent Twin Study in Sweden[a], Colorado Twin Registry, East Flanders Prospective Twin Survey, Finntwin12[a], Finntwin16[a], Gemini Study[a], Guinea-Bissau Twin Study[a], Hungarian Twin Registry, Italian Twin Registry[a], Japanese Twin Cohort[a], Korean Twin-Family Register, Longitudinal Israeli Study of Twins, Michigan Twins Study, Minnesota Twin Family Study, Minnesota Twin Registry, Mongolian Twin Registry, Norwegian Twin Registry, Peri/Postnatal Epigenetic Twins Study[a], Qingdao Twin Registry of Children, Quebec Newborn Twin Study[a], Swedish Young Male Twins Study of Adults[a], Swedish Young Male Twins Study of Children[a], Twins Early Developmental Study[a], West Japan Twins and Higher Order Multiple Births Registry[a] and Young Netherlands Twin Registry[a]. All twin cohorts were used in the analyses on the association between birth weight and later height (total sample). [a]Twin cohorts used in the analyses involving birth length. MZ, monozygotic twins; DZ, dizygotic twins.

height in each age group (179 paired observations). Taken together, we had 224,818 observations (112,409 paired observations), 55% MZ and 45% same-sex DZ, from 83,704 twin individuals (41,852 complete twin pairs). For analyses of birth length, we additionally removed twins without information on birth length (43,487 individuals), birth length < 25 or > 60 cm (25 individuals), unmatched pairs (410 individuals) or intra-pair difference in birth length > 12 cm (10 twin pairs), resulting in 72,692 paired observations (19,881 complete twin pairs). Finally, we calculated PI [weight (kg)/height (m^3)] as a measure of relative weight at birth; we additionally removed those individuals with PI < 12 or > 38 or intra-pair difference in PI > 15 kg/m^3 resulting in 71,881 paired observations (19,612 complete twin pairs).

All participants were volunteers and they or their parents gave informed consent when participating in their original studies. A limited set of observational variables and anonymized data were delivered to the data management center at University of Helsinki. The pooled analysis was approved by the ethical committee of Department of Public Health, University of Helsinki.

2.2. Statistical analyses

Statistical analyses were conducted using the Stata statistical software package (version 12.0; StataCorp, College Station, Texas, USA). First, all height measurements were adjusted for exact age within each age and sex group using linear regression (height was used as the dependent variable and age as a continuous independent variable) and the resulting residuals were used as the input variables for the following analyses. Since all analyses were carried out separately for birth weight,

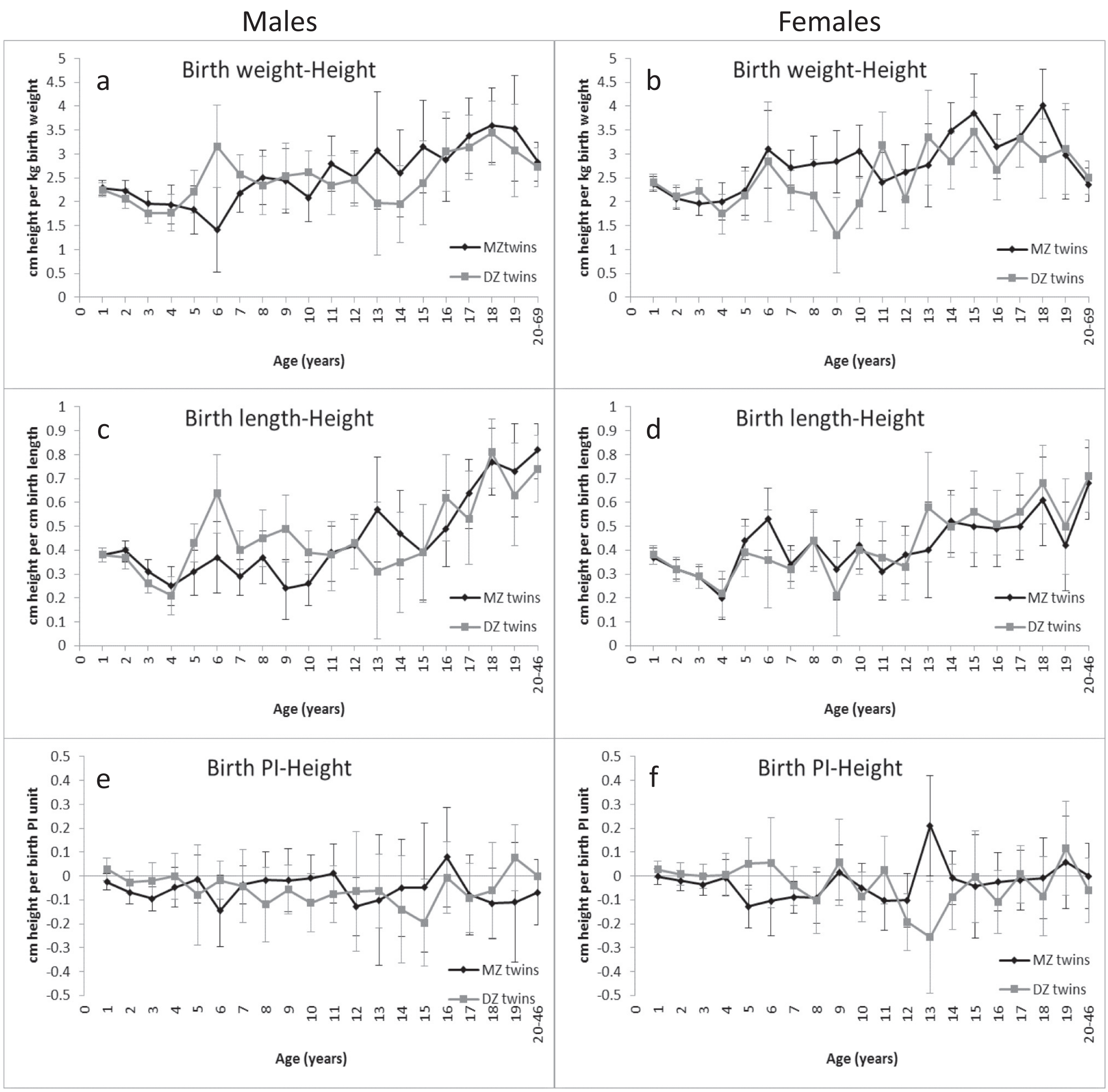

Fig. 1. Regression coefficients with 95% confidence intervals for the associations between birth size and later height, with monozygotic (MZ) and dizygotic (DZ) twins treated as individuals (individual level). Birth size (weight, length or PI) was used as the explanatory variable, height as the outcome, and birth year and twin cohort as additional regressors. For birth weight and length, associations are significant at $p < 0.001$ with the following exceptions (**$p < 0.01$, *$p < 0.05$): a (MZ6**), b (DZ9**), c (DZ13*, DZ14**), d (DZ6**, DZ9*). For birth PI, p-values are provided in Appendix Table 7.

length and PI, in the description of the methods we refer to birth size for simplicity.

Even though the primary focus is on within-pair analyses, we studied the association between birth size and height residuals at both the individual and within-pair level for comparison. At the individual level, linear regression models for each age, sex and zygosity group were used with birth size as the explanatory variable and height residuals as the outcome. Associations were adjusted for birth year and twin cohort (treated as continuous and categorical variables, respectively). The non-independence within twin pairs was taken into account by using the cluster-option available in Stata [30]. This method takes into account that twin pairs rather than independent individuals are sampled and accordingly corrects the standard errors to be larger because of the less informative sample design. For the within-pair analyses, intra-pair differences in birth size were calculated by randomly subtracting the twin with the smallest size at birth from the co-twin with the largest size at birth or vice versa; the twin order was the same for the calculation of intra-pair differences in later height. This guarantees an approximately normal distribution of the new variables. We then performed linear regression models for each age, sex and zygosity group with intra-pair birth size difference as the explanatory variable and intra-pair height residuals difference as the outcome. The associations were also adjusted for birth year and twin cohort. Next, we ensured that the regression lines passed through the origin by checking that the intercept was not different from zero.

An interaction analysis was performed to investigate whether zygosity influenced the associations between birth size and height residuals by introducing a product term of zygosity and birth size (weight or length) into the regression model. At the individual level, linear regression models for each age and sex group were used with height

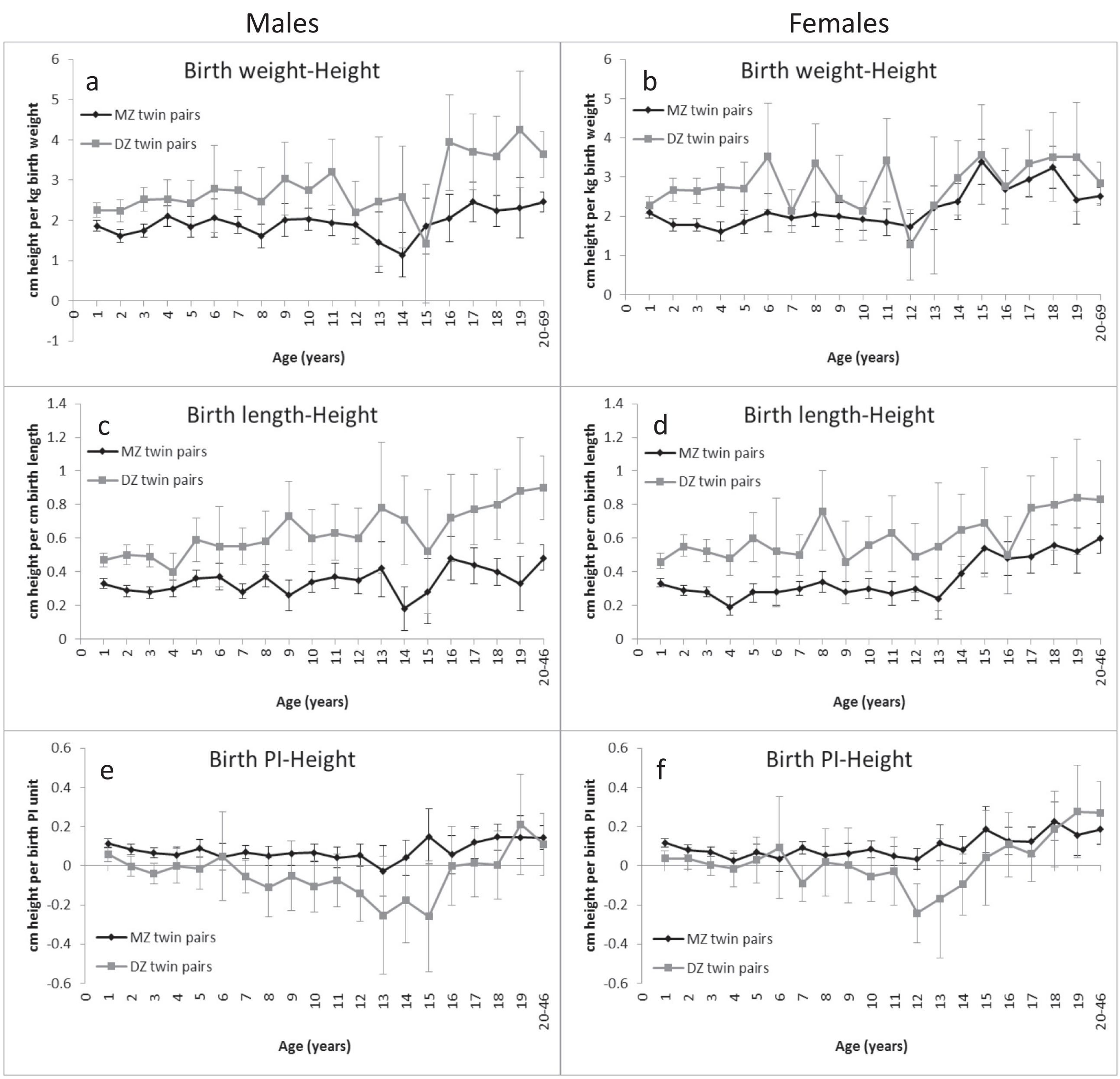

Fig. 2. Regression coefficients with 95% confidence intervals for the associations of intra-pair differences in birth size with intra-pair differences in later height, in monozygotic (MZ) and dizygotic (DZ) twin pairs (within-pair level). Intra-pair birth size (weight, length or PI) difference was used as the explanatory variable, intra-pair height difference as the outcome, and birth year and twin cohort as additional regressors. For birth weight and length, associations are significant at $p < 0.001$ with the following exceptions (**$p < 0.01$, *$p < 0.05$, #NS): a (DZ13**, DZ15#), b (DZ12**, DZ13*), c (MZ14**, MZ15**, DZ15**), d (DZ6**, DZ13**). For birth PI, p-values are provided in Appendix Table 7.

residuals as the outcome, and birth size, zygosity, the product term of zygosity and birth size, birth year and twin cohort as the regressors. At the within-pair level, linear regression models for each age and sex group were performed with intra-pair height difference as the outcome, and intra-pair birth size difference, zygosity, the product term of zygosity and intra-pair birth size difference, birth year, and twin cohort as the regressors. Further, the quadratic effect of birth size was investigated by introducing the term in the regression models for the association between birth size and height residuals, that is, by introducing the quadratic term of birth size (weight or length) in the individual level analyses and the quadratic term of intra-pair birth size differences in the pair-wise analyses. Finally, since all analyses were based on height residuals, we refer to "height residuals" as "height" for simplicity, except in statistical methods section.

3. Results

3.1. Descriptive statistics

Descriptive statistics for birth size and height by zygosity, sex and age are provided in Table 1. Mean birth weight and length were slightly greater in males than in females and in DZ than in MZ twins. The SD of birth weight was also greater in males and DZ twins, but the SD of birth length was very similar in the four sex and zygosity groups. PI showed a very similar mean across sex and zygosity groups and a slightly greater SD in DZ twins. Regarding height, sample size for each zygosity, age, and sex group ranged between 662 and 6860 measurements. The age 6 and 19 years groups had the smallest sample sizes. Mean height was expectedly greater with age in both sexes, with the exception of the slightly shorter mean height observed at age 20–69 years, which reflects differences in the distribution of different cohorts within each age group. Mean values were greater in males than in females; only at the age of 11 and 12 years were girls somewhat taller than boys, reflecting the earlier onset of pubertal growth in girls. The SD of height was generally greater with age until it peaked at 12 years in girls and at 13 years in boys, and then lower with age. DZ twins had slightly greater mean height than MZ twins in both sexes, but the SD of height did not show any clear zygosity pattern.

3.2. Test for quadratic effect

We first tested the quadratic effect of birth size on the associations. At the individual level, a quadratic effect of birth weight was observed only at age 1 (Appendix Table 1); the quadratic term of birth length was significant at several ages, but the effect size was very small (Appendix Table 2). In the pair-wise analyses, only 7 and 10 of 80 tests for birth weight and length, respectively, reached nominal significance ($p < 0.05$), but after Bonferroni correction for multiple testing, none were significant ($p_{corrected} < 0.001$) (Appendix Tables 3 and 4). Since the primary focus of the present study is on within-pair analyses, the quadratic effect of birth size was not included in the models.

3.3. Individual level analyses

At the individual level, birth weight was positively associated with later height at all ages in both sexes; each 1-kg increase in birth weight was associated with 1.30 (95% CI 0.51–2.09) to 4.01 (95% CI 3.24–4.78) cm taller height (Fig. 1). Birth length was also positively associated with later height: a 1-cm increase in birth length was associated with from 0.21 (95% CI 0.13–0.29) to 0.82 (95% CI 0.70–0.93) cm greater height. In contrast, PI at birth was not generally associated with later height. For both birth weight and length, the magnitude of the associations was similar in males and females and was somewhat more pronounced in late adolescence and adulthood than in childhood. Supported by the lack of interaction between zygosity and birth weight or length (only 3 and 2 of 40 tests had p-value < 0.05, respectively) (Appendix Tables 1 and 2), the magnitude of the associations was similar in MZ and DZ twins.

3.4. Within-pair level analyses

Within twin pairs, intra-pair differences in birth size were also positively associated with intra-pair differences in later height: each 1-kg difference in birth weight and 1-cm difference in birth length was associated with 1.14 (95% CI 0.59–1.69) to 4.25 (95% CI 2.81–5.70) and 0.18 (95% CI 0.05–0.31) to 0.90 (95% CI 0.71–1.09) cm taller height, respectively (Fig. 2). Supported by the zygosity interaction effects found at several ages (Appendix Tables 5 and 6), particularly for birth length, the magnitude of the associations in DZ twins was greater than in MZ twins at several ages. This difference in the magnitude between zygosities was more pronounced for birth length; the greatest differences were observed mainly in adolescence and adulthood for boys and in childhood for girls. Moreover, since some of the previous studies in twin pairs were based on samples that are also part of the CODATwins project, we repeated the analyses excluding those samples and obtained very similar results (data not shown). Finally, intra-pair PI differences were not generally associated with intra-pair height differences in DZ twins, but showed significant and positive associations at several ages in MZ twins.

4. Discussion

The present study, based on a multinational database of 28 twin cohorts, showed that birth weight and length are positively associated with later height in males and females from infancy to adulthood. Because the associations within DZ pairs were generally greater than within MZ pairs, our results support the role of genetic and individual-specific environmental factors in the relationship and refine previous findings by considering, in addition to adult age, childhood and adolescence using one-year age groups from 1 to 19 years of age.

At the individual level, our findings are in line with previous twin and singleton studies in adolescence and adulthood showing that an increase in 1-kg birth weight and 1-cm birth length was associated with 3.3–4.0 cm and 0.73–0.92 cm taller height, respectively [9,24,25,27,31]. At the within-pair level, intra-pair differences in both birth weight and length were associated with intra-pair differences in later height in both zygosity groups. The relationships in MZ twin pairs showed that individual-specific environmental factors are important in the association between birth size and later height. Our results are comparable with those from other studies of MZ twin pairs in adolescence and adulthood, which reported regression coefficients ranging 1.9–3.3 cm height/kg birth weight [23–27] and 0.45–0.73 cm height/cm birth length [24,26]. The magnitude of associations between PI and later height observed at some ages within MZ pairs (up to 0.2 cm/PI unit) is similar to that reported for Finnish twins [26]. These individual-specific environmental factors could be related to intrauterine differences experienced by twin pairs who are discordant for birth size, for example differences in delivery of nutrients to the fetus. It has been suggested that intrauterine programming in response to fetal malnutrition induces permanent changes in structure and function of the body, which may cause shorter height in later life [17]. This is in accordance with a randomized trial in East Java showing that energy supplementation during pregnancy increased postnatal growth and reduced malnutrition in preschool children [32].

As in our multinational database, the previous studies on birth weight and length also found greater associations in DZ twin pairs ranging 3.6–4.4 cm height/kg birth weight [23–26] and 0.84–0.96 cm height/cm birth length [24,26], suggesting that genetic factors are involved in the relationship between birth size and later height. This is supported by the strong genetic correlation (0.41) observed between birth weight and adult height in European ancestry samples using linkage-disequilibrium score regression based on information from genome-wide association studies of common genetic variants [33], as well as by studies showing that previously reported adult height loci [34] show genome-wide associations with both birth weight [33] and length [35]; this evidence indicates that the effects of height related loci on growth start prenatally and persist into adulthood. Moreover, there was some evidence that genetic factors are more important in the association with birth length than with birth weight, which was also observed in Finnish twins [26], but not in Dutch twins [24]. Together with the lack of association between PI (a measure of relative weight) and later height within DZ pairs suggesting that genetic factors are not involved, our findings suggest that the association between birth weight and later height is largely driven by birth length, particularly the part of the association explained by genetic factors.

We observed that the importance of genetic and individual-specific environmental factors on the associations between birth size and later height somewhat differed by age at height measurement, sex and birth size indicator. The magnitude of the intra-pair associations in both MZ and DZ twins generally increased with age, but comparisons with previous studies are not possible because they did not analyze these associations in childhood. It has been suggested that, although the effects of the fetal period tend to persist in later life, the etiology of the association shifts during puberty and young adulthood towards a larger genetic influence [19,26]. Our study supports this finding only for boys. It is important to note that twins can also be distinguished on placentation; approximately two thirds of MZ twin pairs are monochorionic and thus the co-twins share the same placenta, whereas DZ twin pregnancies are always dichorionic. An unequal placental sharing is a major cause of fetal growth discordance in MZ twins [36]. Although findings are inconsistent, some chorionicity effects have been reported for height in childhood [36]. Therefore, it could be argued that placental differences between monochorionic and dichorionic MZ twins [36,37] may increase the intra-pair associations in MZ pairs, and thus provide evidence for enduring intrauterine effects. However, this could not be tested because the lack of data on placentation in these cohorts.

The main strength of the present study is the large sample size of our multinational database of twin cohorts with information on both birth weight and length and height measures from infancy to adulthood. We performed an individual based pooled analysis to provide results for this sample including the large majority of existing twin cohorts having information on birth size. Generalization for the global population is, however, not possible because countries or regions are not equally represented and the database is heavily weighted towards Caucasian populations following the westernized lifestyle. Another limitation of the data is that most of the measures were parentally reported (birth measures) and self-reported or parental-reported (height measures) [28]. However, the accuracy between maternal recall and medical records of birth weights (in singletons) have reached a high kappa value (0.89) [38], and the correlations between measured and self-reported heights have commonly been over 0.90 [39,40]. Moreover, there are many potential sources of error both for birth weight and birth length. It is not likely that they would explain the observed associations, i.e. the measurement errors of birth size would correlate with the measures of later height, but they may make the observed associations weaker. Finally, it has been questioned whether differences in birth size in twins are a suitable model for differences in birth size in general, because intrauterine growth in twins is different from that in singletons and fetal growth may be particularly compromised in MZ twins [41]. However, the magnitude of the relationship between birth weight and height in twins was similar to that reported in singletons [9], and thus there is no reason to suggest that data from twins cannot be used to shed light on causal pathways underlying these associations also in the general population.

In conclusion, our findings showed that both genetic and individual-specific environmental factors influence the association between birth size and later height from infancy to adulthood. Although the magnitude somewhat differed by sex and age at height measurement, genetic factors were in general more importantly involved in the association with birth length than with birth weight. The influence of individual-specific environmental factors on the association supports the role of the intrauterine environment in the development of later height, and suggests that improvement of the intrauterine delivery of nutrients may in part prevent growth problems during childhood and adolescence leading to shorter stature in adulthood.

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Appendix A. Supplementary data

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References

[1] G.D. Batty, M.J. Shipley, D. Gunnell, R. Huxley, M. Kivimaki, et al., Height, wealth, and health: an overview with new data from three longitudinal studies, Econ. Hum. Biol. 7 (2009) 137–152.
[2] A. Deaton, R. Arora, Life at the top: the benefits of height, Econ. Hum. Biol. 7 (2009) 133–136.
[3] Emerging Risk Factors Collaboration, Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis, Int. J. Epidemiol. 41 (2012) 1419–1433.
[4] K. Silventoinen, J.L. Baker, T.I.A. Sørensen, Growth in height in childhood and risk of coronary heart disease in adult men and women, PLoS One 7 (2012) e30476.
[5] T.A. Paajanen, N.K. Oksala, P. Kuukasjarvi, P.J. Karhunen, Short stature is associated with coronary heart disease: a systematic review of the literature and a meta-analysis, Eur. Heart J. 31 (2010) 1802–1809.
[6] K. Silventoinen, S. Zdravkovic, A. Skytthe, P. McCarron, A.M. Herskind, et al., Association between height and coronary heart disease mortality: a prospective study of 35,000 twin pairs, Am. J. Epidemiol. 163 (2006) 615–621.
[7] S. Wiren, C. Haggstrom, H. Ulmer, J. Manjer, T. Bjorge, et al., Pooled cohort study on height and risk of cancer and cancer death, Cancer Causes Control 25 (2014) 151–159.
[8] N.J. Binkin, R. Yip, L. Fleshood, F.L. Trowbridge, Birth weight and childhood growth, Pediatrics 82 (1988) 828–834.
[9] D.S. Seidman, R. Gale, D.K. Stevenson, A. Laor, P.A. Bettane, et al., Is the association between birthweight and height attainment independent of the confounding effect of ethnic and socioeconomic factors? Isr. J. Med. Sci. 29 (1993) 772–776.
[10] J. Bacallao, M. Amador, M. Hermelo, The relationship of birthweight with height at 14 and with the growing process, Nutrition 12 (1996) 250–254.
[11] J. Karlberg, Z.C. Luo, Foetal size to final height, Acta Paediatr. 89 (2000) 632–636.
[12] H.T. Sørensen, S. Sabroe, K.J. Rothman, M. Gillman, F.H. Steffensen, et al., Birth weight and length as predictors for adult height, Am. J. Epidemiol. 149 (1999) 726–729.
[13] T. Tuvemo, S. Cnattingius, B. Jonsson, Prediction of male adult stature using anthropometric data at birth: a nationwide population-based study, Pediatr. Res. 46 (1999) 491–495.
[14] P. Rantakallio, L. von Wendt, Prognosis for low-birthweight infants up to the age of 14: a population study, Dev. Med. Child Neurol. 27 (1985) 655–663.
[15] I. Paz, D.S. Seidman, Y.L. Danon, A. Laor, D.K. Stevenson, et al., Are children born small for gestational age at increased risk of short stature? Am. J. Dis. Child 147 (1993) 337–339.
[16] J. Leger, C. Levy-Marchal, J. Bloch, A. Pinet, D. Chevenne, et al., Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study, BMJ 315 (1997) 341–347.
[17] Barker DJP, Mothers, Babies and Health in Later Life, 2nd ed., Churchill Livingstone, Edinburgh, UK, 1998.
[18] R.S. Strauss, Effects of the intrauterine environment on childhood growth, Br. Med. Bull. 53 (1997) 81–95.
[19] D. Boomsma, G. Willemsen, E. Geus, N. Kupper, D. Posthuma, R. IJzerman, et al., Twins and the Fetal Origins Hypothesis: An Application to Growth Data. Hormones and the Brain, Springer-Verlag Berlin, Heidelberg, 2005, pp. 29–46.
[20] R. Morley, T. Dwyer, Studies of twins: what can they tell us about the fetal origins of adult disease? Paediatr. Perinat. Epidemiol. 19 (Suppl. 1) (2005) 2–7.
[21] I. Blickstein, L.G. Keith, D.M. Keith, Multiple Pregnancy, 2nd ed., Taylor and Francis Group, London and New York, 2005.
[22] D.B. Allison, F. Paultre, S.B. Heymsfield, F.X. Pi-Sunyer, Is the intra-uterine period really a critical period for the development of adiposity? Int. J. Obes. Relat. Metab. Disord. 19 (1995) 397–402.
[23] J. Baird, C. Osmond, A. MacGregor, H. Snieder, C.N. Hales, et al., Testing the fetal origins hypothesis in twins: the Birmingham twin study, Diabetologia 44 (2001) 33–39.
[24] R.G. IJzerman, C.D. Stehouwer, M.M. Van Weissenbruch, E.J. De Geus, D.I. Boomsma, Evidence for genetic factors explaining the association between birth weight and low-density lipoprotein cholesterol and possible intrauterine factors influencing the association between birth weight and high-density lipoprotein cholesterol: analysis in twins, J. Clin. Endocrinol. Metab. 86 (2001) 5479–5484.
[25] R.J. Loos, G. Beunen, R. Fagard, C. Derom, R. Vlietinck, Birth weight and body composition in young adult men—a prospective twin study, Int. J. Obes. Relat. Metab. Disord. 25 (2001) 1537–1545.
[26] K.H. Pietiläinen, J. Kaprio, M. Räsänen, A. Rissanen, R.J. Rose, Genetic and environmental influences on the tracking of body size from birth to early adulthood, Obes. Res. 10 (2002) 875–884.
[27] R.J. Loos, G. Beunen, R. Fagard, C. Derom, R. Vlietinck, Birth weight and body composition in young women: a prospective twin study, Am. J. Clin. Nutr. 75 (2002) 676–682.
[28] K. Silventoinen, A. Jelenkovic, R. Sund, C. Honda, S. Aaltonen, et al., The CODATwins project: the cohort description of collaborative Project of Development of Anthropometrical Measures in Twins to study macro-environmental variation in genetic and environmental effects on anthropometric traits, Twin Res. Hum. Genet. 18 (2015) 348–360.
[29] A. Jelenkovic, Y. Yokoyama, R. Sund, K. Pietiläinen, Y.M. Hur, et al., Association between birth weight and later body mass index: an individual based pooled analysis of 27 twin cohorts participating in the CODATwins project, Int. J. Epidemiol. 46 (2017) 1488–1498.
[30] R.L. Williams, A note on robust variance estimation for cluster-correlated data, Biometrics 56 (2000) 645–646.
[31] K.H. Pietiläinen, J. Kaprio, M. Räsänen, T. Winter, A. Rissanen, et al., Tracking of body size from birth to late adolescence: contributions of birth length, birth weight, duration of gestation, parents' body size, and twinship, Am. J. Epidemiol. 154 (2001) 21–29.
[32] J.A. Kusin, S. Kardjati, J.M. Houtkooper, U.H. Renqvist, Energy supplementation during pregnancy and postnatal growth, Lancet 340 (1992) 623–626.
[33] M. Horikoshi, R.N. Beaumont, F.R. Day, N.M. Warrington, M.N. Kooijman, et al., Genome-wide associations for birth weight and correlations with adult disease, Nature 538 (2016) 248–252.
[34] A.R. Wood, T. Esko, J. Yang, S. Vedantam, T.H. Pers, et al., Defining the role of common variation in the genomic and biological architecture of adult human height, Nat. Genet. 46 (2014) 1173–1186.
[35] R.J. van der Valk, E. Kreiner-Moller, M.N. Kooijman, M. Guxens, E. Stergiakouli, et al., A novel common variant in DCST2 is associated with length in early life and height in adulthood, Hum. Mol. Genet. 24 (2015) 1155–1168.
[36] K. Marceau, M.T. McMaster, T.F. Smith, J.G. Daams, C.E. van Beijsterveldt, et al., The prenatal environment in twin studies: a review on chorionicity, Behav. Genet. 46 (2016) 286–303.
[37] R.J.F. Loos, C.L. Ridgway, K.K. Ong, Theoretical underpinning of the use of twin studies in life course epidemiology, in: D.A. Lawlor, G.D. Mishra (Eds.), Family Matters: Designing, Analysing and Understanding Family Based Studies in Life Course Epidemiology, Oxford University Press, Oxford, 2009, pp. 57–84.
[38] M.C. McCormick, J. Brooks-Gunn, Concurrent child health status and maternal recall of events in infancy, Pediatrics 104 (1999) 1176–1181.
[39] M. Giacchi, R. Mattei, S. Rossi, Correction of the self-reported BMI in a teenage population, Int. J. Obes. Relat. Metab. Disord. 22 (1998) 673–677.
[40] M.L. Rowland, Self-reported weight and height, Am. J. Clin. Nutr. 52 (1990) 1125–1133.
[41] R. Morley, Can we generalise from findings in twins? Paediatr. Perinat. Epidemiol. 19 (Suppl. 1) (2005) 54–59.